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LETTER TO THE EDITOR

Risk of hepatitis B reactivation following baricitinib or tocilizumab for treatment of COVID-19

Hong Foo[1] · Fiona Phan[2] · Melissa Bagatella[2] · Irene Petrovski[3] · Vana Nagendra[1] · Priya Acharya[3] · Miriam Levy[2,4] · Emilia Prakoso[2,5]

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Reactivation of hepatitis B (HBV) is a well-documented risk associated with certain immunosuppressive drugs [1]. Baricitinib, a janus kinase inhibitor, and tocilizumab, an interleukin-6 (IL-6) receptor antagonist, are immunomodulatory drugs which have been used with systemic corticosteroids as short course treatment of patients with moderate to severe COVID-19. While hepatitis B reactivation has been reported with these medications [2, 3], data regarding the risk of reactivation in the COVID-19 setting is limited. As such, various conflicting recommendations exist regarding the use of antiviral hepatitis B prophylaxis in this setting [4–7], particularly in patients with resolved hepatitis B infection [8].

In this prospective observational cohort study conducted from July 2021 to March 2022 at Liverpool and Campbelltown Hospitals, Sydney, Australia, we sought to determine the risk of hepatitis B reactivation in patients with resolved hepatitis B infection following treatment with baricitinib or tocilizumab for COVID-19.

Hospitalised patients aged 18 years or older were enrolled in the study based on the following inclusion criteria: SARS-CoV-2 RNA positivity on respiratory tract sample, serological evidence of resolved hepatitis B infection (positive hepatitis B core antibody (anti-HBc) and negative hepatitis B surface antigen (HBsAg)), and receipt of baricitinib or tocilizumab in conjunction with dexamethasone for treatment of COVID-19. Dosing of medications was as per guidelines at the time: oral baricitinib 4 mg daily for up to 14 days (adjusted for renal impairment), single-dose weight-based tocilizumab, and dexamethasone 6 mg daily (daily dose prednisolone equivalents 40 mg) for up to 10 days. Duration of medications was at the discretion of the treating clinician. Patients were monitored with liver function tests and hepatitis B serology (HBsAg and hepatitis B surface antibody (HBsAb)) at weeks 6, 12, and 24 following receipt of baricitinib or tocilizumab. Hepatitis B reactivation was defined as HBsAg seroreversion (switch in HBsAg from negative to positive), with HBV DNA performed in patients who seroreverted during follow-up.

A total of 157 patients who received baricitinib or tocilizumab for treatment of COVID-19 had evidence of resolved hepatitis B infection. Two patients were receiving long-term antiviral prophylaxis for hepatitis B in the context of chronic immunosuppression (one liver transplant recipient and one multiple myeloma patient on chemotherapy). Due to the lack of consistent guidelines regarding the need for antiviral prophylaxis at the time, five patients were initiated on treatment with entecavir at the discretion of the treating clinician. Of the 150 patients who did not receive antiviral prophylaxis, 29 patients (19.3%) died after a mean of 11 days (range 0–32 days) following treatment with baricitinib or tocilizumab. The majority of deaths (27/29, 93%) were related to COVID-19.

The remaining 121 patients were recommended to undergo blood test monitoring. Follow-up data were available in a final study cohort of 54 patients. Sixty-seven patients were lost to follow-up because they were uncontactable or failed to proceed with blood tests. Patients were predominantly male (33/54, 61%), with a mean age of 64 years (range 33–87 years); the main ethnic groups were South Pacific (28%), Middle Eastern (26%), and South-Eastern/

✉ Hong Foo
hong.foo@health.nsw.gov.au

1 Department of Microbiology and Infectious Diseases, NSW Health Pathology – Liverpool, Sydney, Australia

2 Department of Gastroenterology, Liverpool Hospital, Sydney, Australia

3 Department of Gastroenterology, Campbelltown Hospital, Sydney, Australia

4 University of New South Wales, Sydney, Australia

5 Central Clinical School, The Faculty of Medicine & Health, University of Sydney, Sydney, Australia

South Central Asian (26%). There were no HIV or hepatitis C co-infections. One renal transplant recipient was receiving long-term immunosuppression with prednisone 5 mg daily, mycophenolate, and tacrolimus.

At baseline, 50/54 patients (93%) had a HBsAb level ≥ 10 IU/L, and the mean alanine transaminase (ALT) was 61 U/L (range 11–305 U/L). Forty-seven patients received baricitinib (mean duration 8.7 days, range 1–27 days), and seven patients received tocilizumab (median dose 800 mg, range 600–800 mg). The mean duration of high dose corticosteroids (daily dose prednisolone equivalents > 20 mg) was 12 days (range 7–35 days).

In the 54 study patients who had blood tests results available at any follow-up timepoint, no HBsAg seroreversion was detected in: 31 patients at 24 weeks (mean ALT 30 U/L, range 12–101; HBsAb ≥ 10 IU/L in 90%), 35 patients at 12 weeks (mean ALT 27 U/L, range 8–76; HBsAb ≥ 10 IU/L in 80%), and 34 patients at 6 weeks (mean ALT 33, range 10–96; HBsAb ≥ 10 IU/L in 79%), following treatment with baricitinib or tocilizumab (Figure. 1). Seventeen patients had complete data at all monitored time points (6, 12, and 24 weeks).

A previous prospective cohort study from Rodriguez-Tajes et al. [6] similarly found a low risk of hepatitis B reactivation amongst 19 patients with resolved hepatitis B infection who received short course immunomodulatory agents with an IL-6 inhibitor (tocilizumab or siltuximab) for COVID-19 in the absence of antiviral prophylaxis. No cases of HBsAg seroreversion were detected after 1–2 months, a follow-up period which was comparatively shorter than our study. Two patients with HBsAb < 10 IU/L were found to have detectable HBV DNA at follow-up, although this was below the quantifiable limit.

The strengths of our study include the long follow-up period, with blood test monitoring at multiple timepoints. In addition, we report outcome data for patients with resolved hepatitis B treated with short course baricitinib, which has not previously been reported. Our study was limited by the small sample size and high loss to follow-up, reflecting the challenges of real-world data collection, where asymptomatic patients likely felt the surveillance blood tests were unnecessary. Serologic rather than virologic monitoring for hepatitis B reactivation was performed in our study patients due to the national Medicare criteria restricting rebates for HBVDNA testing to HBsAg-positive patients. Lack of virological monitoring may have potentially missed HBVDNA reactivation in

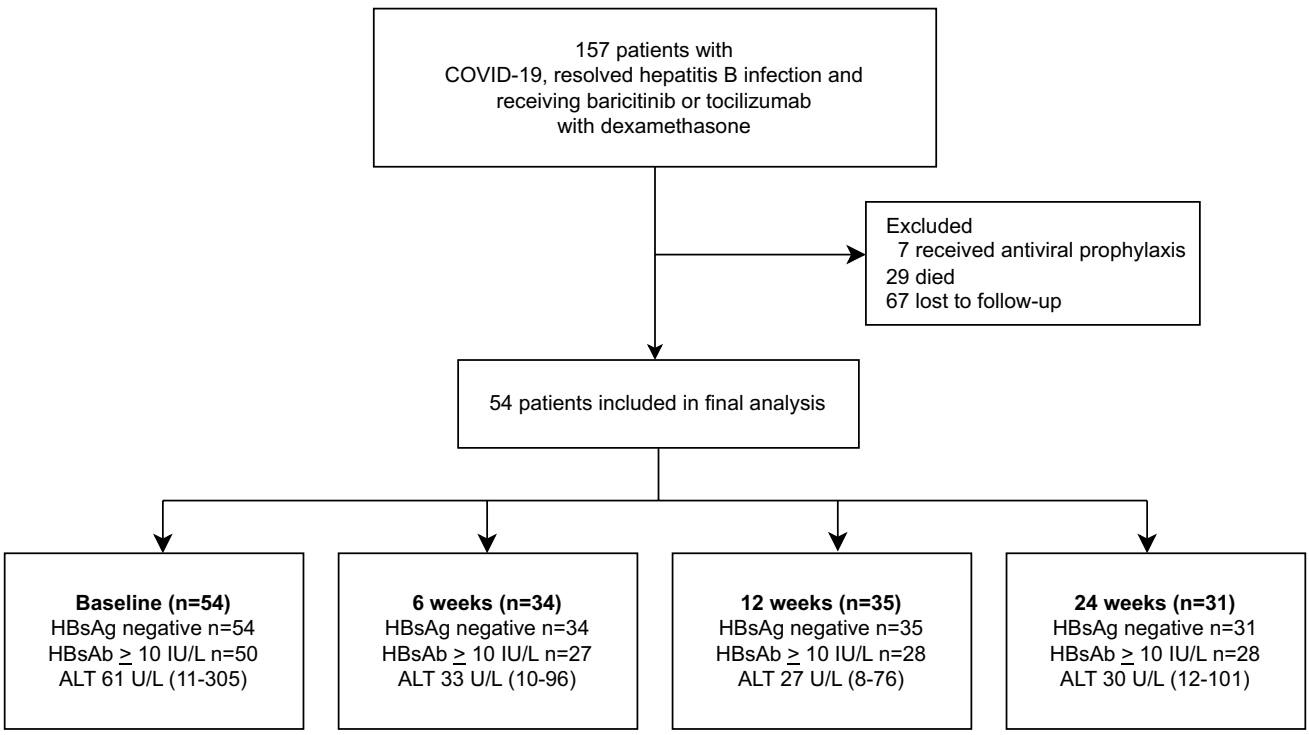

Fig. 1 Flowchart of patient selection and outcomes

patients who otherwise remain HBsAg negative. However, given the maintenance of a protective HBsAb level (≥ 10 IU/L) in the majority of patients, clinically significant HBV DNA reactivation would seem unlikely.

The risk of hepatitis B reactivation (HBsAg seroreversion) in our study cohort of patients with resolved hepatitis B who received short course baricitinib or tocilizumab with dexamethasone for treatment of COVID-19 without antiviral prophylaxis was low, and normalisation of mean ALT occurred during a follow-up period of up to 24 weeks. Routine antiviral prophylaxis in this setting may not be required. Routine follow-up may be of low yield and may not be cost-effective. Larger studies are required to confirm this finding.

Author contribution All authors read and approved the final manuscript.

Data availability The datasets generated during and/or analysed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Declarations

Ethics approval Approval was granted by the Southwestern Sydney Local Health District Human Research Ethics Committee.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare no competing interests.

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